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Filed : July 17, 2001

REMARKS

Claims 10-28 have been rejected. Claims 10-20 are presently cancelled. This is not a surrender of subject matter and Applicants reserve the right to pursue the subject matter of these claims at a later point in time.

Claims 21-38 are currently pending. New dependent Claims 29-38 have been added. Support for the new claims can be found throughout the application, for example, in Figures 3, 4, 6, and 7 and paragraphs 0039, 0049 0076, 0079, and 0082 (of the published application). No new matter has been added.

Applicants appreciate the Examiner's withdrawal of the prior objections and/or rejections and for the opportunity for the telephonic interview summarized above.

The claimed invention is nonobvious over the combination of Zanzucchi, Okano, and Brenner

The Examiner has asserted that Claims 10-28 are obvious over the combination of Zanzucchi (U.S. Pat. No. 5,593,838), Okano (U.S. Pat. No. 5,607,646), and Brenner (U.S. Pat. No. 5,962,228). The Examiner found that the claimed invention encompasses "two different capture moieties... bound at two different locations on a support that... can act as a flow path for a mixture of nucleic acids capable of flowing." Applicants respectfully traverse the rejection and disagree with the Examiner's characterization of the claimed invention; the actual elements are recited in the claims.

As the Examiner is aware, three criteria must be met in order to establish a *prima facie* case of obviousness.

First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

(M.P.E.P. §2143). However, the combined cited art does not teach all of the recited elements. Furthermore, a proper motivation to combine the three references has not been supplied. Finally, for the reasons noted below, the combination of at least one of the references with the others, as recited in the Office Action, is improper. As such, a *prima facie* case of obviousness has not been established.

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Moreover, as appreciated by the Examiner, in considering obviousness four factual inquires must be performed. One must (A) determine the scope and content of the prior art, (B) ascertain the differences between the prior art and the claims in issue, (C) resolve the level of ordinary skill in the pertinent art, and (D) evaluate evidence of secondary considerations. (*Graham v. John Deere*, 383 U.S. 1, 148 USPQ 459 (1966)). As explained below, the cited art does not teach all of the elements in the claims, actually teaches away from some of the Examiner's proposed modifications or combinations of the elements, and does not establish that there is a reason or goal in the art that generally relates to combining the above specific elements in the manner claimed. Furthermore, there appears to be substantial differences between the technology of the cited art and the currently claimed invention. For example, there is a serial aspect in the presently claimed invention that is simply not appreciated in the cited art. This has many benefits for the presently claimed method. As such, Applicants submit that the claimed invention is nonobvious.

Applicants note that Claims 10-20 have been cancelled, rendering the rejections regarding those claims moot. As such, only the issues relevant to Claims 21-28 (and new Claims 29-37) are addressed herein.

Okano does not teach selectively adjusting the temperature between electrodes.

Okano has been cited for allegedly teaching the use of heat to selectively alter one solid support without altering a second support. Contrary to what is asserted in the Office Action, Okano does not teach or suggest the element of altering the temperature of one solid support without altering the temperature of at least one other solid support. (Office Action, page 5). Rather, as clearly set forth in the remainder of the section cited by the Examiner, and in the rest of the specification, Okano teaches that one can use differences in electrostatic repulsion (where the entire solution is heated) in order to increase or decrease the release DNA. Okano does state that a heated solution can be used to elute the sample; however, when the entire specification is reviewed, it is clear that this heated elution is only in reference to the general solution and is not in reference to the selective elution teachings of Okano. Thus, Okano does not teach or suggest altering the temperature of a selected support while leaving unaltered the temperature of another support. Thus, no reference has been cited in the Office Action that teaches the use of a

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temperature difference between two supports for selective elution. As such, a *prima facie* case of obviousness has not been established with regard to Claim 21 and its dependent claims.

In the Interview Summary, the Examiner has noted that Zanzucchi teaches a heated well. The Examiner appears to be citing this to make up for the heat dependent aspect lacking from Okano. While Zanzucchi does teach that a well can be heated, this teaching is irrelevant to the instantly claimed method. Zanzucchi uses the heated chamber for enzymatic reactions and inactivation. Zanzucchi does not teach or suggest that heat can or should be used to allow binding or remove bound nucleotides in any selective manner. Importantly, neither Zanzucchi nor Okano teaches or suggests changing the temperature of one solid support without changing the temperature of another solid support. Thus, even when this embodiment is considered, none of the cited references teach the use of heat to selectively elute a sequence from one solid support without heating a second solid support. Additionally, the combination of the references does not suggest this either as none of the references address this aspect. As not all of the elements have been taught, a *prima facie* case of obviousness has not been established. Applicants note that the mere fact that one of skill in the art could use various modifications of some of the embodiments of Zanzucchi's device in the claimed method is irrelevant to the issue of patentability of the recited method claim.

Brenner does not teach a linear array.

As noted in the Interview Summary, the Examiner has asserted that the general teaching of an array in Brenner teaches the specific concept of a linear array in which particular clusters of beads or microparticles are arranged into groups (wherein each group possesses the same sequence specific capture agent) and arranged in a linear format. The Examiner appears to be asserting that the specific and explicit teaching of the two-dimensional array in Brenner necessarily teaches the above described concept of a linear array. Applicants respectfully disagree.

It is clear that Brenner means "two-dimensional" array when he refers to "an array." For example, only two-dimensional arrays are depicted (see, e.g., FIGs. 3 and 2A). Additionally, Brenner states, at the end of the background section, that "[a]n important advance in sequencing technology could be made if an alternative approach was available for sequencing DNA... that

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was amenable to simultaneous, or parallel, application to multiple target polynucleotides.” (Emphasis added). Further, nowhere in Brenner is there a depiction of a linear array, or any description of how a linear array would or could be useful or applied in the arrangement shown in FIG. 3. Thus, a plain reading of Brenner indicates that Brenner means a two-dimensional array when Brenner refers to an array. As Brenner does not teach a linear array, not all of the elements have been taught and a *prima facie* case of obviousness has not been established.

Moreover, Applicants note that no teaching, suggestion, or motivation has been supplied to demonstrate why one of skill in the art would have modified the two-dimensional array explicitly taught in Brenner, to make the one-dimensional array suggested by the Examiner. Applicants note that Brenner used the two dimensional array because the technique in Brenner involves the simultaneous analysis of the various microparticles. If anything, Brenner appears to teach away from the use of a linear array by teaching the importance of parallel processing. As appreciated by the Examiner, it is improper to “combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983)” (M.P.E.P. §2145 (X)(D)(2)).

The Examiner’s Proposed Combination of Brenner and Zanzucchi is Improper

The Examiner has attempted to combine or modify the teachings in Brenner, involving a process that is explicitly highly parallel/simultaneous, with a serial embodiment in Zanzucchi in order to obtain an element of the presently claimed invention (e.g., the “mixture flows serially through each of the plurality of solid supports”). Such a combination is improper.

Brenner explicitly states that “[a]n important feature of my invention is the capability of applying the method to many different polynucleotides in parallel...” (col. 3, lines 46-62 of Brenner, emphasis added, *see also*, col. 2, lines 24-30; col. 4, lines 60-67; and col. 7, lines 10-20). Thus, Brenner actually teaches that his microparticles should be used in parallel applications and he teaches away from a serial (or purely linear), application involving the microparticles. It is improper to combine or modify references when their combination would teach away from the invention or render the prior art unsatisfactory for its intended purpose (M.P.E.P. §2145(X)(D)). Not only does Brenner generally teach away from serial embodiments, but the application of Brenner’s microparticles in a serial application would remove the parallel

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aspect taught in Brenner as an important advantage of his invention. As such, the combination of Brenner, or any parallel/simultaneous array system, with Zanzucchi, is clearly improper.

There is No Motivation for Combining a) Okano and b) Brenner and/or Zanzucchi

Applicants note that the Examiner, while relying on Okano for some teachings, has supplied no motivation for why one of skill in the art would have used the cited teachings of Okano in combination with Brenner and/or Zanzucchi. Applicants respectfully remind the Examiner that, in order to establish a *prima facie* case of obviousness, there must be at least some motivation to combine each reference. In the instant Office Action, no motivation is provided. As such, a *prima facie* case of obviousness has not been established.

Furthermore, one of skill in the art would not have been motivated to make the Examiner's proposed combination because the substrate (microparticles) in the Brenner reference would be redundant to the substrate (electrode surface) in the Okano reference. In particular, if one were to combine the electrodes of Okano (which acts as a support for DNA in Okano) with the wells of Zanzucchi, there would be no reason or motivation (in the prior art) to further add microparticles (that act as a support for DNA) to the device. This is because Okano's electrodes already serve as a solid support. Thus, the addition of microparticles would be redundant to Okano's electrode. Because it would be redundant, one of skill in the art would not have been motivated to combine these aspects as asserted by the Examiner. Indeed, absent hindsight, there appears to be no reason to have made the combination that the Applicants have made in the claimed invention. As appreciated by the Examiner, hindsight and the use of the Applicants' own disclosure are not permitted in a rejection under 35 U.S.C. §103.

The proposed motivation to combine Brenner and Zanzucchi is inadequate

The Examiner's asserted "motivation" to combine Brenner and Zanzucchi, noted in the Interview Summary, is inadequate to establish that one of skill in the art would have combined the two references. The Examiner has merely noted that Zanzucchi can be used in a DNA hybridization assay. However, as the Examiner is aware, the mere possibility that two references can be combined is insufficient to establish that one of skill in the art would have been motivated to combine specific aspects disclosed in the references. In the instant case, the mere fact that

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Zanzucchi can be used in some DNA hybridization assays and that Brenner can be used in DNA hybridization assays supplies no motivation for the combination and modification of particular subparts of Brenner (a two-dimensional microparticle array system having sections in the array that are clusters of identical tag sequences) into a well format taught in Zanzucchi (which also is modified).

In summary, the Examiner has either failed to provide or has provided inadequate or improper motivations for combining the various components noted in the cited references. As such, a *prima facie* case of obviousness has not been established.

The Examiner has supplied no support for the contention that the device in Okano could be used to alter the physical properties of the separate microparticles of Brenner.

Applicants note that there is no support cited in the Office Action to indicate that the microparticles in Brenner could be used in conjunction with the selective elution mechanism taught by Okano simply by adding them to a well that included Okano's electrodes. While Applicants acknowledge that the state of the art is well-developed, there is simply no evidence to suggest that such a combination would be expected to work. Applicants respectfully note that it is the Examiner's burden to establish a reasonable expectation of success in such a combination.

In particular, Okano does not teach the selective heating of one solid support without heating a second solid support. Rather, Okano merely teaches the use of a heated liquid across the entire surface. Thus, there is no disclosure for how to heat one support without heating a second support. As such, Applicants submit that the skilled artisan would have had no expectation of success in the combination proposed by the Examiner.

As appreciated by the Examiner, the dependent claims, while nonobvious for the reasons noted above in regard to the independent claims, also recite additional elements that further distinguish them from the cited art.

Because not all of the elements have been taught, there is no motivation to combine the cited references, and the Examiner has not demonstrated that one of skill in the art would have expected the combination to work, a *prima facie* case of obviousness has not been established.

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Furthermore, under 35 U.S.C. §103(a) and the Graham v. John Deere Co. test the claimed invention is nonobvious over the cited art because of the actual teachings in the cited art and the differences between the cited art and the claimed invention. As such, Applicants request that the rejection be withdrawn and the claims allowed.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that the pending claims are in condition for allowance and request the same. If, however, some issue remains that the Examiner feels can be addressed by Examiner Amendment, the Examiner is cordially invited to call the undersigned for authorization.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: 2/12/07

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